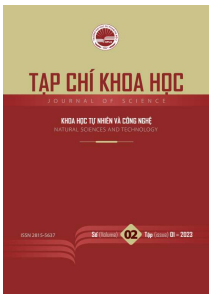
HPU2 Journal of Sciences:
Natural Sciences and Technology

journal homepage: https://sj.hpu2.edu.vn




*Article type: Research article*

# Synthesis of new triazole-fused bicyclic heterocycles involving benzofuran from 4-amino-1,2,4-triazole-3-thiol

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**Abstract**

In the further research and synthesis of hybrid molecules which exhibit highly biological activities, the synthesis of triazole-fused bicyclic heterocycles bearing the benzofuran has been undertaken. A facile, convenient and good yielding synthesis of novel benzofuran-bearing 1,2,4-trazole derivatives were described. Herein, two derivatives of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole were synthesized from salicylaldehyde in four steps in moderate to good yields. Structures of all the targeted synthesized compounds were elucidated by spectral methods of analysis.

***Keywords:*** Benzofuran, 1,2,4-triazole, 4-amino-1,2,4-triazole-3-thiol, [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, triazole-fused bicyclic, heterocycles

## 1. Introduction

1,2,4-Triazole derivatives have attracted researchers because of their important chemical and biological properties. They possess a number of significant biological activities involving antibacterial, antifungal, anti-inflammatory, anticonvulsant, antioxidant, anticancer[1, 2]… Among them, 4-amino-1,2,4-triazole-3-thiol derivatives are of particular interest to scientists because of their significant increase in biological activity due to amino and thiol groups.[3] The derivatives [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (Figure 1) were synthesized from 4-amino-1,2,4-triazole-3-thiol compounds and have important biological activities such as antibacterial,[4] antifungal,[4] anticancer[5, 6] and treatment of Alzheimer's disease[7].

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https://doi.org/10.56764/hpu2.jos.2023.1.2.64-69

Received date: 26-4-2023 ; Revised date: 28-4-2023 ; Accepted date: 28-4-2023

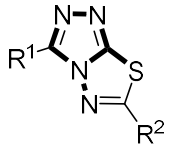


**Figure 1**. Structure of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives

Benzofuran is also widely investigated because of their biological activities including antifungal, antibacterial, antiviral, anti-HIV and anticancer.[8-10] Thus, the combination of these components to form hybrid molecules may exhibit strongly biological potential.[11] They have become a motif for the development of new drugs.

## 2. Materials and methods

### *2.1. General*

All chemicals were purchased from Merck (for synthetic class) and Sigma Aldrich while organic solvents were purchased from the commercial source and were used without any further purification. The NMR spectra were acquired using the Bruker Avance III spectrometer (500 MHz for $^{1}$H and 125 MHz for $^{13}$C). Chemical shifts are expressed in parts per million (ppm) and reported relative to the residual solvent signal as an internal reference. High resolution mass spectra (HRMS) were recorded using a HRMS X500$_R$ QTOF mass spectrometer in electrospray ionization (ESI) mode. The melting points were determined using a Gallenkamp digital Melting point apparatus 5A-6797 with a rate of heating of 2°C/min. Reactions were monitored using thin layer chromatography (TLC) on silica gel plates (silica gel 60 $F_{254}$, Merck), visualized under ultraviolet light (254 nm). Column chromatography was performed on silica gel Merck 60 (230–400 mesh) purchased from HiMedia Laboratories Pvt. Ltd. (India).

### *2.2. Synthesis of ethyl benzofuran-2-carboxylate (**1**)*

A solution of salicylaldehyde (12.2 g, 100 mmol) and $K_2CO_3$ (41.10 g, 300 mol) in DMF (80 mL) was stirred at room temperature for 30 minutes. Then, ethyl chloroacetate (12.25 g, 100 mol) was slowly dropped into that solution while the mixture was stirred during two hours at 80–90 °C. The color of solution was changed from yellow to green, dark green, brown and finally black. Consequently, that solution was poured into crushed ice and was extracted with ethyl acetate (100 mL × 3). Then, the combined organic phases were dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to afford ethyl benzofuran-2-carboxylate **(1)** (15.80 g, 83%).

Dark yellow liquid; $^{1}$H–NMR (500 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 7.75 (*dd*, *J* = 8.0 Hz, 1.1, 1H), 7.67 (*dd*, *J* = 8.4, 1.0 Hz, 1H), 7.65 (*s*, 1H), 7.47 *(ddd*, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.31(*ddd*, *J* = 7.9, 7.2, 1.2 Hz, 1H), 4.32 (*q*, *J* = 7.1 Hz, 2H), 1.30 (*t*, *J* = 7.1 Hz, 3H); $^{13}$C–NMR (125 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 158.6, 155.0, 145.1, 127.7, 126.6, 123.8, 123.0, 113.8, 112.0, 61.0, 13.9. These data are consistent with that reported in the literature.[12]

### *2.3. Synthesis of benzofuran-2-carbohydrazide (**2**)*

A solution of ethyl benzofuran-2-carboxylate **(1)** (11.40 g, 60 mol) in absolute ethanol (30 mL) was slowly continuously added by hydrazine hydrate 50% (18.00 g, 180 mol) under reflux for four hours. Upon completion, the reaction mixture was kept at 2–4 °C overnight to solidify the product. Consequently, the separated solid was filtered, washed with cold ethanol and then recrystallized in absolute ethanol to give benzofuran-2-carbohydrazide **(2)** (7.91 g, 75%).

White crystals, melting point 190–194 °C (lit. [12] 190–194 °C); $^1$H–NMR (500 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 10.01 (*s*, 1H), 7.75 (*dd*, *J* = 8.0, 0.8 Hz, 1H), 7.63 (*dd*, *J* = 8.4, 0.9 Hz, 1H), 7.51 (*s*, 1H), 7.44 (*ddd*, *J* = 8.4, 7.2, 0.8 Hz, 1H), 7.32 (*ddd*, *J* = 8.0, 7.2, 0.9 Hz, 1H), 4.58 (*br,* 2H); $^{13}$C–NMR (125 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 157.8, 154.2, 148.4, 127.0, 126.6, 123.6, 122.6, 111.7, 108.7. These data are consistent with that reported in the literature.[12]

*2.4. Synthesis of 4-amino-5-(benzofuran-2-yl)-4H-1,2,4-triazole-3-thiol (**3**)*

In a 500 mL flask, dissolve the benzofuran-3-carbohydrazide **(2)** (7.40 g, 40 mmol) and KOH (2.24 g, 40 mmol) in absolute ethanol (100 mL). Slowly add $CS_2$ (3.04 g, 40 mmol) to the mixture, stir for 30 min at room temperature. The yellow precipitate is filtered and washed with $Et_2O$ (20 mL × 3). The combined organic layer was dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to obtain the solid product. Dissolve the solid obtained in water (30 mL). The hydrazine hydrate (2.0 mL, 40 mmol) was added into the mixture and heat under reflux for four hours. The reaction mixture was cooled to room temperature and was then acidified using a solution of HCl 1M to pH~6–7 to form a precipitate. The precipitate is filtered and recrystallized in DMF: $H_2O$ (v/v 1: 1) to obtain 4-amino-5-(benzofuran-2-yl)-4H-1,2,4 -triazole-3-thiol (**3**) (6.78 g, 73%).

White crystals; $^1$H–NMR (500 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 14.14 (*s*, 1H), 7.90 (*s*, 1H), 7.83 (*dd*, *J* = 7.9, 1.1 Hz, 1H), 7.71 (*d*, *J* = 8.3 Hz, 1H), 7.46 (*ddd*, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.35 (*dd*, *J* = 7.9, 7.3 Hz, 1H), 5.96 (*s*, 2H); $^{13}$C–NMR (125 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 167.1, 154.0, 142.6, 141.4, 127.1, 126.6, 123.8, 122.5, 111.5, 109.9.

*2.5. General procedure for the synthesis of 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole (**4**)*

A mixture of 4-amino-5-(benzofuran-2-yl)-*4H*-1,2,4-triazole-3-thiol (**3**) (232 mg, 1.0 mmol) and aromatic carboxylic acid (1.2 mmol) in phosphorus oxychloride (10 mL) was heated under reflux for five hours, then cooled to room temperature and poured into cold water. Excess $POCl_3$ was neutralized with potassium carbonate solution. The precipitate formed was filtered, dried and recrystallized from DMF to give compounds **4a-b**.

*3-(Benzofuran-2-yl)-6-phényl-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole* (**4a**): 191 mg, yield: 60%, yellow solid; $^1$H–NMR (500 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 8.14 (*dd*, 7.2, 1.5 Hz, 2H), 7.93 (*s*, 1H), 7.87 (*d*, 7.7 Hz, 1H), 7.80 (*d*, 8.3 Hz, 1H), 7.73 (*m,* 1H), 7.68 (*dd*, 7.7, 7.1 Hz, 2H), 7.49 (*ddd*, 8.3, 7.2, 1.2 Hz, 1H), 7.39 (*dd*, 7.8, 7.2 Hz, 1H).; $^{13}$C–NMR (125 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 167.8, 154.5, 154.4, 141.8, 139.2, 133.2, 129.8, 128.9, 127.5, 127.5, 126.5, 124.0, 122.3, 111.7, 107.8.

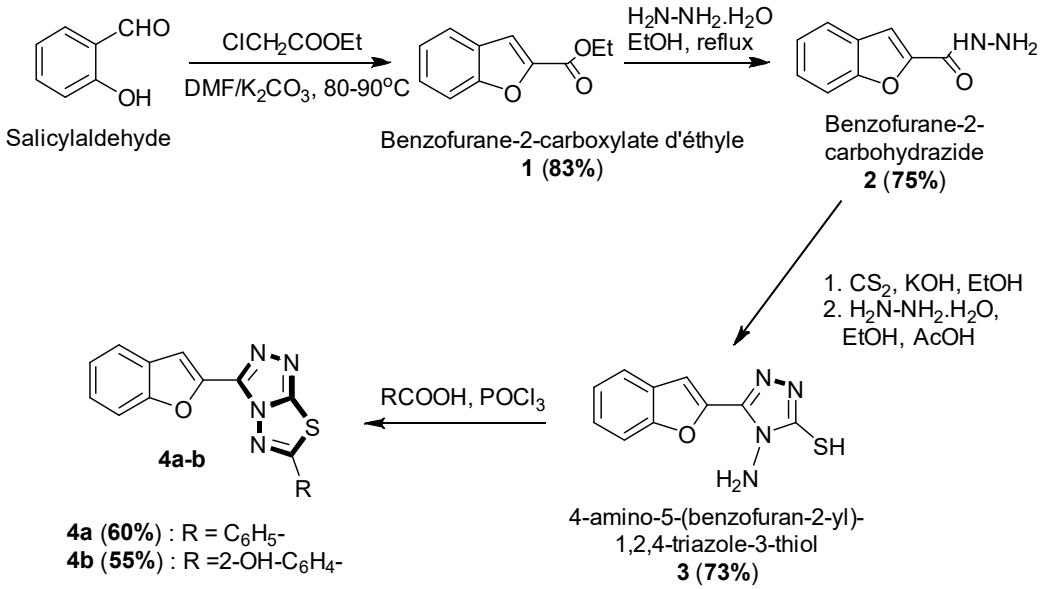
*3-(Benzofuran-2-yl)-[6-(2-hydroxyphényl)]-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole* (**4b**): 184 mg, yield: 55%, dark yellow solid; $^1$H–NMR (500 MHz, DMSO-$d_6$) $\delta_H$ (ppm): 10.41 (*s*, 1H), 7.95 – 7.88 (*m*, 2H), 7.85 (*d*, *J* = 7.6 Hz, 1H), 7.81 (*d*, *J* = 8.2 Hz, 1H), 7.56 – 7.49 (*m*, 2H), 7.41 (*t*, *J* = 7.6 Hz, 1H), 7.13 (*d*, *J* = 8.4 Hz, 1H), 7.06 (*t*, *J* = 7.6 Hz, 1H); $^{13}$C–NMR (125 MHz, DMSO-$d_6$) $\delta_C$ (ppm): 163.4, 156.7, 156.5, 155.1, 140.2, 133.8, 129.2, 127.3, 127.1, 124.3, 122.7, 119.8, 117.2, 111.9, 110.6, 109.4. HR-MS (ESI): calcd. For $C_{17}H_{10}N_4O_2S$ ($[M-H]^-$) 333.0446, found: 333.0447.

## 3. Results and discussion

The 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**4a, 4b**) were synthesized according to **Scheme 1**. Ethyl benzofuran-2-carboxylate (**1**) is prepared from salicylaldehyde, potassium carbonate, and ethyl chloroacetate in the solvent dimethylformamide. This mixture is heated at 80-90 °C for 6 hours. The product (**1**) obtained with 83% yield. Then, (**1**) is converted to benzofuran-2-carbohydrazide (**2**) by the reaction with hydrazine hydrate with the yield of 75%. Hydrazide (**2**) reacts

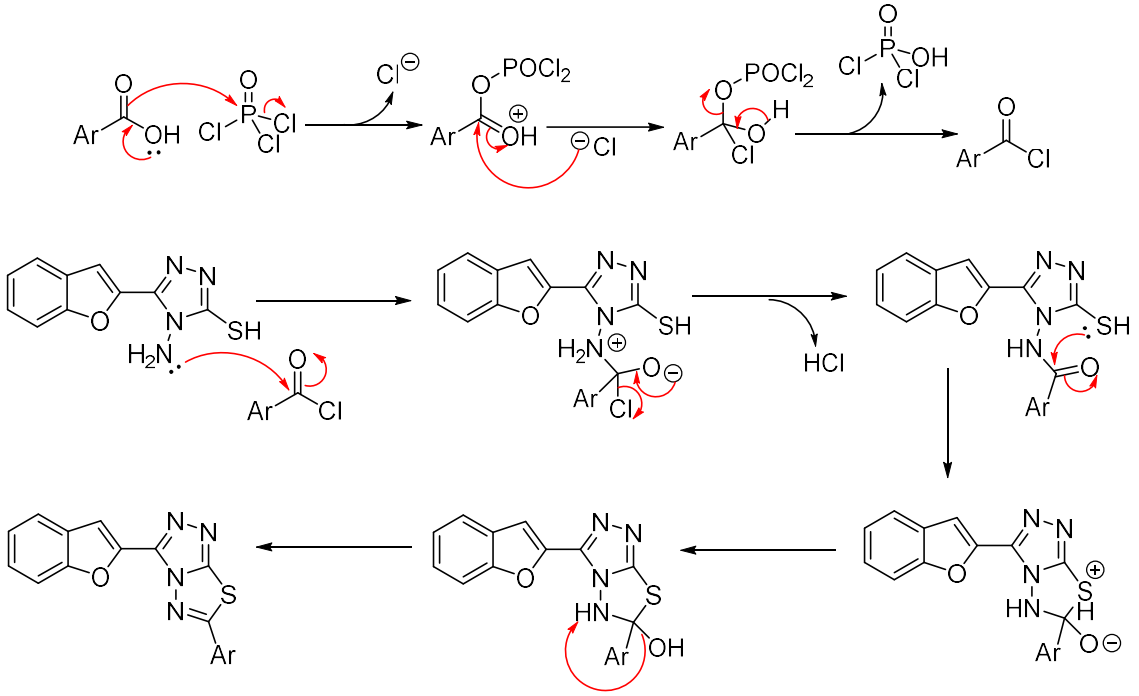
with carbon disulfide ($CS_2$) and hydrazine hydrate successively to form 4-amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (**3**) with 73% yield.

The important step of this synthetic pathway is cyclization between 4-amino-5-(benzofuran-2-yl)-*4H*-1,2,4-triazole-3-thiol (**3**) and carboxylic acid. We obtained two 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **4a-b** with the yields ranging from 55 to 60%. The chemical structures of these products were elucidated using the $^1H$ and $^{13}C$ NMR spectra. The disappearance of mobile protons N**H**$_2$ (about 6 ppm) and S**H** (about 14 ppm) in the $^1H$–NMR spectrum of each derivative allowed us to confirm the successful cyclization. Furthermore, in the $^{13}C$-NMR spectra, the presence of carbon N=**C**-S at about 163-168 ppm were further supportive of this structure.




**Scheme 1**. The synthetic route for the preparation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives

A possible reaction mechanism for the formation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives has been proposed as shown in **Scheme 2**. First, carboxylic acid reacts with $POCl_3$ to form acid chloride. Then, the amino group attacks the carbonyl group, followed by the leaving of a chloride to afford an amide. The cyclization reaction occurs between the thiol group and carbonyl group, followed by dehydration to form 1,3,4-thiadiazole derivatives.



**Scheme 2**. Proposed reaction mechanism of the formation of 3-(benzofuran-2-yl)-6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives.

The electronic properties of the substituents on the aromatic ring of carboxylic acids play a role in their reaction performance. In the presence of an electron donating substituent (–OH), its resonance donating to the aromatic ring reduces the activity of the carbonyl group. This reason leads to the formation of products **4b** with a slightly lower yield (55%) than that of product **4a** (60%) in the case of a non-substituent (R=H).

## 4. Conclusions

Using a convenient and simple method, starting from salicylaldehyde, we have synthesized two 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives in four steps. First, the salicylaldehyde was transformed to ethyl benzofuran-2-carboxylate (**1**), which was subsequently treated with hydrazine hydrate to afford benzofuran-2-carbohydrazide (**2**), with the yields of 77% and 80%, respectively. The treatments of benzofuran-2-carbohydrazide with carbon disulfide and potassium hydroxide in ethanol affords an ntermediate product which reacts later with hydrazine hydrate to obtain the 4-amino-5-(benzofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol (**3**) with 73% yield. The key cyclization step between the 4-amino-1,2,4-triazole-3-thiol (**3**) with carboxylic acids was carried out to form the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **4a** and **4b** with the yields of 60% and 55%, respectively. The obtained results can be explained by the effect of the substituent on the aromatic ring of carboxylic acid. The electron donating substituent (–OH) due to its resonance donating to the aromatic ring could reduce the activity of carbonyl group, leads to the cyclization with a slightly lower yield. Their chemical structures were elucidated through NMR and HR–MS spectral analysis. All 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives are new compounds, reported for the first time. Due to the ability to combine with other frameworks, the synthesis of 1,2,4-triazine derivatives is still very promising and developing widely.

## Declaration of Competing Interest

The authors declare no competing interests.

## Author contributions

Thanh-Tu Bui performed the experiments and interpreted the NMR and MS data. Hoang-Uy Tan and Hoang-Danh Nguyen collected the bibliography and analyzed the experimental data of the synthesis. Tan Tai Nguyen designed the research, wrote the first draft, reviewed and edited the manuscript and supervised the investigation. All the authors have read and approved the content of the final manuscript.

## Acknowledgments

This research is funded by University of Science, Vietnam National University – Ho Chi Minh City under grant number U2022-19. We thank Truong Thi My Thoai and Nguyen Tran Hoang Thi for their contribution to the synthesis experimental work.

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